

**REMARKS**

Following entry of the foregoing reply, claims 44 and 69 to 73 will be pending in the present application.

***Withdrawal of Terminal Disclaimer***

Pursuant to 37 C.F.R. § 1.182 and M.P.E.P. § 1490, Applicants submit herewith a petition for withdrawal of the terminal disclaimer that was filed on November 17, 2005 over U.S. Pat. No. 6,326,199 B1. The terminal disclaimer is no longer applicable since it addressed a rejection that had been entered with respect to claims that have since been withdrawn from the instant patent application. Accordingly, Applicants respectfully request that the terminal disclaimer also be withdrawn.

***Rejection Under § 103(a) For Alleged Obviousness***

Claims 44 and 69-73 have been rejected for alleged obviousness over the combined teaching of four references, *i.e.*, Uhlmann & Peyman, Chemical Reviews, The American Chemical Society, June 1990, Vol. 90, No. 4, pp. 543-578 (“the Uhlman reference”), PCT Pub. No. WO/1991/010671 (“the Cook publication”), Secrist et al., J. Med. Chem. 1991, Vol. 34, pp. 2361-2366 (“the Secrist reference”), and U.S. Pat. No. 5,354,656 to Sorge et al. (“the Sorge patent”). Applicants respectfully request reconsideration of this rejection because the Office Action does not identify any reason why the various teachings of the cited references would have led those of ordinary skill to a claimed invention.

The Office has argued that, given that “the general benefits of alpha-nucleoside or 4'-thionucleoside modifications in oligonucleotides were known in the art”, and in view of the cited references, “[a]bsent evidence to the contrary, one of ordinary skill in the art, at the time of the instant invention[,] would have been motivated to design the claimed oligonucleotides according to the present invention” (3/6/2007 Office Action at page 5). Applicants respectfully submit that the Office’s conclusion is not based on any particular findings that one skilled in the art would have selected the cited references for combination; rather, all that

has been provided is the Office's bare assertion based upon the hindsight provided by Applicants' own disclosure.

The mere fact that those skilled in the art would have been able to make the posited modification falls far short of establishing obviousness under Section 103. For example, M.P.E.P. § 2143.01(IV) cautions that statements describing modifications to a cited reference as being "well within the ordinary skill of the art" are not sufficient to establish a *prima facie* case of obviousness. Indeed, the level of skill in the art cannot be relied upon to provide the suggestion to modify references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999). There must be some suggestion or motivation to make such modifications. *See* M.P.E.P. § 2143.01 (III).

When viewed in this context, the cited references cannot fairly be said to render Applicants' claimed inventions obvious because there is no evidence of record demonstrating that those of ordinary skill would have been motivated to actually combine the references' respective teachings or to do so in a way that would have produced a claimed invention. Although the Office Action asserts "one of ordinary skill in the art, at the time of the instant invention[,] would have been motivated to design the claimed oligonucleotides" (3/6/2007 Office Action at page 5), there is no evidence or reasoning of record as to why those of ordinary skill would have had such motivation. Absent evidence or reasoning demonstrating that the posited modifications of the cited references would have been ones that those of ordinary skill in the art actually would have been motivated to make, the rejection of claims 44 and 69-73 for alleged obviousness is improper and should be withdrawn. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'"). *See also* MPEP § 2142 ("The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness."); *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan,

with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed”); *May 3, 2007 Memo from Margaret A. Focarino, Deputy Commissioner for Patent Operations, U.S. Patent Office* (“it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.”) (commenting on *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. at \_\_ (Apr. 30, 2007) (No. 04-1350)).

***Rejection Under § 112, First Paragraph***

Claims 44 and 69-73 have been rejected for alleged failure to comply with the written description requirement because the instant specification allegedly does not provide support for a compound having either consecutively linked  $\alpha$ -nucleosides or consecutively linked 4'-thionucleosides (*see* 3/6/2007 Office Action at page 6, lines 1-4). Applicants respectfully disagree.

In Example 2A, the instant specification describes an oligonucleotide comprising a “4 nucleotide long region of  $\alpha$ -nucleotides” (*see* page 29, lines 3-4). Therefore, in at least this instance, the instant specification clearly discloses a compound having consecutively linked  $\alpha$ -nucleosides.

In Example 7, the instant specification describes an oligonucleotide comprising 4'-thionucleotide regions flanking a central 2'-deoxy phosphorothioate nucleotide region (*see* page 32, lines 13-20). The specification provides that “[i]n the manner of Example 6, a region of 4'-thionucleotides is prepared” (*see* page 32, lines 16-18). Example 6 describes an oligonucleotide comprising carbocyclic surrogate nucleosides flanking a central 2'-deoxy phosphorothioate nucleotide region, in which “a first region of 4 carbocyclic nucleosides . . . is prepared” (*see* page 31, line 29 to page 32, line 8). Therefore, Example 7 (which substitutes 4'-thionucleotides for the carbocyclic surrogate nucleosides of Example 6) describes an oligonucleotide comprising a region of four 4'-thionucleotides. Contrary to the view of the Office, in at least the instance of Example 7, the instant specification clearly discloses a compound having consecutively linked 4'-thionucleosides.

**DOCKET NO.:** ISIS-5213  
**Application No.:** 10/601,242  
**Office Action Dated:** March 6, 2007

**PATENT**

Applicants therefore respectfully submit that the Office's rejection under § 112, first paragraph is inapposite and should be withdrawn.

\* \* \* \* \*

The foregoing represents a *bona fide* attempt to advance the present case to allowance. In view of the preceding, Applicants respectfully request approval of the attached petition and withdrawal of the rejections of the claims, and further submit that the pending claims are in condition for allowance. If the Examiner has any questions, the Examiner is invited to call the undersigned at (215) 568-3100.

Date: June 5, 2007

/Joseph Lucci/

Joseph Lucci  
Registration No. 33,307

Woodcock Washburn LLP  
Cira Centre  
2929 Arch Street, 12th Floor  
Philadelphia, PA 19104-2891  
Telephone: (215) 568-3100  
Facsimile: (215) 568-3439